

PATENT SPECIFICATION

(11) 1297261

NO DRAWINGS

- (21) Application No. 1935/69 (22) Filed 13 Jan. 1969
 (23) Complete Specification filed 13 Jan. 1970
 (45) Complete Specification published 22 Nov. 1972
 (51) International Classification C07C 103/38 C07D 48/14 A61K 27/00
 (52) Index at acceptance

C2C 220 227 22Y 29X 29Y 30Y 342 34Y 365 36Y
 3A14A3A 3A14A5 591 623 62X 662 790 79Y KP
 A5B 381 38Y 392 410 41Y 482 48Y 493 49Y 503 50Y
 542 54Y 565 56Y 586 58Y 660 66Y

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(54) PHARMACEUTICAL COMPOSITION



(71) We, E. R. SQUIBB & SONS INC., a corporation organized and existing under the laws of the State of Delaware, United States of America, Lawrenceville-Princeton Road, Princeton, New Jersey 08540, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention provides, as a new substance, a complex of phenazone (andipyrine; 2,3 - dimethyl - 1 - phenyl - 3 - pyrazolin-5 - one) with paracetamol (acetaminophen; 4'-hydroxy-acetanilide).

The phenazone-paracetamol complex provided by the invention is highly suitable and effective for pharmaceutical use, particularly as an analgesic and/or antipyretic, and apart from the phenazone-paracetamol complex itself, the invention also provides a pharmaceutical composition comprising the complex in admixture with a pharmaceutical carrier.

When dry the phenazone-paracetamol complex is a white crystalline powder which contains the phenazone and paracetamol in approximately equimolar proportions in a hydrogen-bonded complex. It has a melting range of 108°—112°C, it has a discrete infrared spectrum corresponding to the two components and on examination by thin layer chromatography it can be shown to be comprised of phenazone and paracetamol only.

The phenazone-paracetamol complex of the invention may be produced by fusing the two substances by direct heating. Alternatively the two substances may be dissolved or dispersed in water or other solvent and the complex crystallises out from the solution; the complex is then collected by filtration and dried.

If desired the solvent may be heated before or after the addition to it of the phenazone and paracetamol, so as to facilitate dissolution, after which the solution is cooled (or

allowed to cool) so that the complex crystallises out from it.

Instead of water an organic solvent such as acetone or alcohol may be used, the solvent being evaporated off after formation of the complex has occurred. Equimolar proportions of paracetamol and phenazone are preferably used for formation of the complex by direct heating of the mixture or for precipitation of the complex from organic solvents, since if either is used in excess this excess must be removed to obtain the pure complex. This can be done easily (but at the expense of extra work) if there is an excess of phenazone since this is soluble in water and could be removed by recrystallisation and washing, but removal of an excess of paracetamol is more difficult. It is better not to have to remove an excess of either compound but to mix them in equimolecular proportions.

If the complex is prepared in aqueous solution equimolecular proportions are again preferred, although an excess of phenazone causes no problem. The two components are put into hot water and the complex then crystallises out. If an excess of phenazone is present, this remains in solution and is simply removed from the complex when the solid complex is separated from the liquid. Paracetamol, however, is insoluble in water and if this component is present in excess, the excess remains in suspension in the aqueous medium and is more difficult to remove from the complex.

The complex of the invention contains the paracetamol and phenazone in approximately a 1:1 molar ratio. On a weight basis the paracetamol content is in the range from 41% to 47% and the phenazone content from 59% to 53%.

The phenazone-paracetamol complex may be used as an analgesic and antipyretic for the relief of pain and fever in warm-blooded animals, including man. The complex may be compounded according to conventional pharmaceutical practice in forms for oral

[Price 25p]

administration, for example tablets, capsules or suspensions containing 100 to 500 mg. of the phenazone-paracetamol complex per tablet or capsule or per 5 ml. of fluid, along with conventional excipients, binders, lubricants, and flavour, as required. In the case of man, administration may be at the rate of 500 to 4000 mg. per day, in single or divided doses.

In carrying out acetic acid writhing tests in mice, it was found that the oral ED_{50} for the phenazone-paracetamol complex was 162 mg/kg, compared with an ED_{50} greater than 400 mg/kg for paracetamol alone. The onset of analgesic action was earlier, and the duration of analgesic action was longer for the complex. In addition, the acute oral LD_{50} in mice for the complex was found to be 1000 mg/kg, midway between the LD_{50} for phenazone and paracetamol individually, showing that toxicity is not more than additive in effect. ("ED₅₀" is the mean "effective dose", meaning the dose which is effective in 50% of the subjects in a sample, while "LD₅₀" is the mean "lethal dose", meaning the dose which is lethal in 50% of the subject in a sample.) The following examples serve to illustrate the invention:—

Example 1

13.8g of phenazone and 15.1g of paracetamol (i.e. equimolecular proportions) are mixed and heated on an oil bath until the mix melts (110°C — 112°C). A portion of the mix is poured on to an enamel tray and permitted to set into a "glass". The remainder of the melt is stirred until cold. Each portion of solid phenazone-paracetamol complex is broken up into a crystalline powder. Yield=99%. M.P. of the glass= 109° — 110°C ; M.P. of the portion cooled with stirring= 110° — 111°C .

Example 2

188.2g of phenazone are dissolved in 100 ml. of distilled water at 50°C . 151.16g of paracetamol are added and dissolved. A viscous solution results. On cooling to room temperature, phenazone-paracetamol complex crystallises out. This crystalline phenazone-paracetamol complex is dried under high vacuum at a temperature less than 40°C . Yield=98%. M.P.= 109.5° — 110°C . Assay: paracetamol 42.7% w/w, phenazone 54.7% w/w.

Example 3

37.6g of phenazone are dissolved in 65 ml. of distilled water at room temperature. 15.1g of paracetamol are added portionwise whilst stirring. Phenazone-paracetamol complex crystallises out. Stirring is continued for 30 minutes. The crystals are filtered and dried under high vacuum at a temperature less than 40°C . M.P.= 108.5° — 109.5°C . Yield=40%, the excess phenazone remaining in solution.

Example 4

18.8g of phenazone and 15.1g of paracetamol are mixed with 75.0 ml. of acetone and boiled on a water bath to effect solution. The heating is continued until the turbulence of the solution becomes sluggish. The solution is then stirred until cold, resulting in a dry, granular powder. This phenazone-paracetamol complex is dried in a vacuum oven to remove residual traces of acetone. Yield=98%. M.P.= 109° — 110.5°C .

Example 5

18.8g of phenazone are dissolved in 25.0 ml. of 95% ethanol at 40°C . 15.1g of paracetamol are added and dissolved. The solution is poured on to a watch glass and most of the alcohol evaporated off. On cooling, phenazone-paracetamol complex crystals precipitate. The crystals are filtered off and dried in a vacuum oven. Yield=66%. M.P.= 111° — 112°C . Assay: paracetamol 42.4% w/w.

Example 6

500 g of phenazone are dissolved in 1 litre of distilled water at room temperature with stirring. Paracetamol is added portionwise to the solution with stirring, allowing each portion to dissolve before adding the next. When the phenazone-paracetamol complex starts to crystallise out, addition of the paracetamol, which has then reached 187g, is discontinued. Stirring is continued for 30 minutes to ensure complete precipitation. The crystals of the complex are filtered off using a Buchner funnel and high vacuum at a temperature less than 40°C . The complex is then recrystallised three times from the minimum quantity of boiling water. The results at each stage are as follows:—

Unrecrystallised material

M.P. 108.5° — 110°C .
Assay: Paracetamol 41.6% w/w.
Phenazone 56.3% w/w.

First recrystallisation

M.P. 110° — 111°C .

Second recrystallisation

M.P. 108° — 110°C .

Third recrystallisation

M.P. 108° — 109°C .

Assay: Paracetamol 46% w/w.
Phenazone 52% w/w.

Example 7

4,000 capsules each containing 500 mg. of phenazone-paracetamol complex are prepared from the following ingredients:

Phenazone-paracetamol complex
(prepared by a method
analogous to that described in
Example 1)
Starch Paste (20% solids)
Magnesium Stearate

2000g
350g
30g

The complex is screened through a 20 mesh screen, dampened with starch paste and the mix is then put through a 20 mesh screen. The mix is then dried at 50°C for 1 hour in a fluid bed drier and then put through a 16 mesh screen. The magnesium stearate is put through a 60 mesh screen, added to the mix and mixed in planetary mixer. The resulting mixture is encapsulated in No. 0 gelatin capsules each containing 525 mg of mix, equivalent to 500 mg of complex.

Example 8

A mix is prepared as described in Example 7. This mix is encapsulated in No. 2 gelatin capsules each containing 165mg of mix, equivalent to 157.1 mg. of complex. (This makes 12,700 capsules.)

Example 9

Tablets, each containing 500 mg. of phenazone-paracetamol complex are prepared from the following ingredients:

Phenazone-paracetamol complex
(prepared by a method
analogous to that described in

Example 1)	1000g
Polyvinyl-pyrrolidone	25g
Alcohol	150ml
Magnesium carbonate	175g
Methyl cellulose	87g
Magnesium stearate	13g

The polyvinyl-pyrrolidone is dissolved in the alcohol. The complex is granulated with this solution and passed through a 12 mesh screen and dried in a fluid-bed drier until dry (about 1 hour). The granules are reduced through a 16 mesh screen and the magnesium carbonate, methyl cellulose and magnesium stearate are added. The whole is mixed in a planetary mixer and pressed to a weight of 650 mg using a $\frac{1}{2}$ inch deep concave punch. The mixture makes 1000 tablets each containing 500 mg of the complex.

Example 10

Tablets each containing 250 mg of phenazone-paracetamol complex are prepared from the following ingredients:

Phenazone-paracetamol complex	250.0g
Polyvinyl pyrrolidone	5.0g
Corn Starch	15.0g
Talc	4.0g
Magnesium stearate	6.0g

The phenazone-paracetamol complex is mixed with half of the corn starch. The polyvinyl pyrrolidone is dissolved in water. The solution is used to granulate the corn starch-complex. Water is added for granulation. The wet granulate is screened through a 4 mesh screen and dried at 50°C. The dried granulate

is then screened through a 16 mesh screen. The remaining half of the corn starch, the talc and the magnesium stearate are added to the dried and screened granulate and the mixture is blended in a planetary mixer. This is then compressed using a $\frac{11}{32}$ inch standard concave punch and die. 1000 tablets of 280 mg. are made, each containing 250 mg. of complex.

We believe that in the phenazone-paracetamol complex prepared in the manner referred to hereinbefore, the respective molecules are loosely bonded to one another by means of hydrogen bonds. Physically the complex behaves as a compound, having well-defined physical properties. When the complex is placed in water in an amount in excess of its limit of solubility, there is some tendency for the complex to break up, but a substantial proportion of the excess remains in suspension in complex form while any paracetamol which is liberated by breakdown of the complex also forms a suspension.

WHAT WE CLAIM IS:—

1. Phenazone-paracetamol complex.
2. A composition comprising phenazone-paracetamol complex and a pharmaceutical carrier therefor.
3. A pharmaceutical dosage unit comprising from 100 to 500 mg. of phenazone-paracetamol complex and a pharmaceutical carrier therefor.
4. A method of alleviating pain in a warm-blooded non-human animal which comprises administering phenazone-paracetamol complex orally to the animal.
5. A process for preparing a complex of phenazone and paracetamol, comprising mixing phenazone and paracetamol, heating the mixture until it melts, cooling the molten mixture (or allowing it to cool) until it sets and breaking up the resulting mass to yield the complex in the form of a crystalline powder.
6. A process for preparing a complex of phenazone and paracetamol, comprising dissolving phenazone and paracetamol in a solvent medium and crystallising the complex from the solution.
7. A process according to claim 6, wherein the solvent medium is heated before or after the addition of the phenazone and paracetamol thereto, so as to facilitate dissolution, and the solution is cooled (or allowed to cool) so that the complex crystallises therefrom.
8. A process according to claim 6 or claim 7, wherein the solvent medium is water.
9. A process according to claim 6 or claim 7, wherein the solvent medium is an organic solvent.
10. A process according to any of claims 5 to 9, wherein the phenazone and paracetamol are used in substantially equimolecular proportions.
11. A process for preparing a complex of

phenazone and paracetamol, substantially as herein described with reference to any of Examples 1 to 6.

- 5 12. Phenazone-paracetamol complex whenever prepared by a process according to any of claims 5 to 11.

13. A pharmaceutical composition or dosage unit, substantially as herein described with reference to any of Examples 7 to 10.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1972.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.